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TITLE: Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide

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14. ABSTRACT
GulfWar (GW) veterans continue to complain of short term memory and mood problems many years following their return from the Persian Gulf. Suspected causes for these health complaints continue to be investigated and include additive and/or synergy stic effects of the varying combinations of exposures to pesticides, pyridostigminebromide(PB), low-level nerve agents, and psychological ltrauma. Many pesticides are neurotoxicantsasare PB and nerve agents. Two subsets of these chemicals, organophosphates(OP)and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. It is the goal of this study to further evaluate the role of pesticides in the development of symptoms reported by GW veterans. This will be accomplished by performing neuropsychological assessments with a group of military pesticide applicators. It is hypothesized that pesticide applicators with high exposures will perform significantly worse on cognitive and neurological measures than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides) will prove to be synergistic and/or additive interms of decreased cognitive and neurological functioning and increased physical symptoms.

15. SUBJECT TERMS
Neuro toxicant exposures, neuropsychological deficits, Gulf War veterans, central nervous system, pesticides, pyridostigminebromide.

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INTRODUCTION

Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Research to date suggests that it is unlikely that there is one single cause for GW illness but rather suggests that multiple causes in different groups of veterans is the likely the cause of continued health symptoms. Suspected causes for GW veterans continued health complaints include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. In our lab, research evaluating the effects of pyridostigmine bromide (PB) exposure on neuropsychological functioning in GW veterans, found significantly lower performance on tasks assessing executive system functioning in the PB exposed GW veterans compared with controls (Sullivan et al., 2003). Pesticide exposure has been associated with mood decrements and residual effects many years after exposure in a large longitudinal cohort of GW veterans (White et al., 2001). In addition, potential low-level nerve agent exposure (from Khamisiyah weapons arsenal) has been associated with mood complaints and executive system decrements in GW veterans (White et al., 2001).

It has been documented that many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. For example, studies of agricultural workers and professional pesticide applicators have found lasting deficits in neurological and cognitive functioning resulting in decreased processing speed and mood complaints (Stephens et al., 1995; Steenland et al., 1994).

It is the goal of this study to further evaluate the role of pesticides in the development of CNS symptoms reported by GW veterans and to assess the additive and/or synergistic effects of combinations of chemical exposures and stress. This will be accomplished by assessing a group of military pesticide applicators with known chemical exposures. It is hypothesized that applicators with high exposures will perform significantly worse on specific cognitive and neurological measures and report more health symptom complaints than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides, low-level nerve agents) will be synergistic and/or additive in terms of decreased cognitive and neurological functioning.

The specific aims of this study are: (1) To determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans (2) To determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans (3) To assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

Body

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide.

Task 1. Develop Plan for Subject Recruitment Months 1-6:

a. Locate and obtain previous exposure interviews from a group of Gulf War veteran pest-control interviewees (PCI) previously contacted by Office of the Special Assistant to the Under Secretary of Defense for GW illnesses (OSA) in 1997-1998 (months 1-3).
b. SRBI, an independent contracting company (with an 80% success rate) will contact all PCIs and obtain current address and administer a brief follow-up questionnaire (months 3-4).
c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure (months 3-5).
d. Identify pool of potential subjects for each of four exposure categories to recruit (months 4-5).
e. Screen potential subjects for exclusion criteria (months 5-6).

Task 2. Perform Subject Recruitment and Data Collection Months 6-42:

a. Study coordinator will contact potential subjects for recruitment and arrange for travel to multiple study sites (months 6-42).
b. Perform cognitive evaluations and psychodiagnostic interviews from 160 study participants (months 6-42).
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for all study subjects (months 6-42).

Task 3. Data Collection and Interim Analyses, Months 18-42:

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing (months 18-42).
b. Interim Statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically (months 18-42).
c. Exposure assessment analyses for pesticides and PB will be ongoing (months 18-42).
d. Annual reports of progress will be written (12-36).

Task 4. Final Analysis and Report Writing, Months 42-48:

a. Analyze subject characteristics of individuals who were lost to follow-up (months 42-44).
b. Write final study report and prepare manuscripts for submission (months 44-48).

The statement of work for years 1-3 is below. The statement of work for year 1 primarily describes the completion of the start-up phase of the study including obtaining the study sample from a group of pest control interviewees (PCIs) previously interviewed by the Deployment Health Support Directorate (DHSD), to obtain current contact information for the PCIs and administer a brief follow-up questionnaire with these individuals. In year 2, the plan was to recruit 58 study participants for the study protocol including cognitive evaluations, psychological interviews and exposure questionnaires and perform data entry and cleaning, and preliminary analyses of the data. The total recruitment for year 2 was 47 study participants. The recruitment goal for year 3 included 61 study participants (50 for the initial projections and 11 from the year 2 goal). The total recruitment for year 3 was 60 study participants bringing the total recruitment effort to 119 subjects (out of 120 projected).

Statement of work for Years 1, 2 and 3:

Task 1. Develop a Plan for Subject Recruitment (as stated above):

a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly the OSA) conducted in 1997-1998.
b. Contract with an outside survey company, SRBI, to contact PCIs and obtain current address and administer a brief follow-up questionnaire.
c. Categorize PCIs into high and low exposure groups based on the telephone surveys.
d. Identify pool of potential subjects for each of four exposure categories to recruit.
e. Screen potential subjects for exclusion criteria.

Task 2. Perform Subject Recruitment and Data Collection (specific to year 3):

a. Recruitment of 61 additional study subjects and arrange for travel to multiple study sites
b. Perform cognitive evaluations and psychodiagnostic interviews with 61 additional study participants
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 61 additional study subjects by study questionnaires.

Task 3. Data Collection and Interim Analyses

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing
b. Interim statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically.

c. Exposure assessment analyses for pesticides and PB will be ongoing.

d. Annual reports of progress will be written.

Task 1a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly OSAGWI) conducted in 1997-1998.

The Pesticides Environmental Exposure Report (www.gulflink.osd.mil) commissioned by the Deployment Health Support Directorate provided estimates of exposure for general deployed military and separately for pesticide applicators from the Gulf War based on interviews with the current study sample of pesticide applicators and preventive medicine specialists and a review of DOD pesticide records.

The term "pest control interviewee" (PCI) refers to any of the 298 personnel interviewed by the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) in the course of the "preventive medicine" (PM), "delousing," and other interviews described in OSAGWI's Pesticides Environmental Exposure Report. OSAGWI chose to interview these individuals because it was believed that they would be the most likely to have knowledge of pesticide products used in the Army, Navy, Air Force, and Marines. They were identified based on military occupational specialty (MOS) codes. PCIs include physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police, and other pest controllers. OSAGWI has since been renamed the Deployment Health Support Directorate (DHSD).

The current study is an examination of the CNS effects of neurotoxicant exposure in pest control interviewees (PCI) with known neurotoxicant exposures as a result of their tour of duty at the time of the Gulf War. PCI's comprise specific groups of GW veterans likely to fall into high and low categories of pesticide exposure based on their military occupational specialty (MOS) or designation. Each potential participant previously completed a pesticide interview that included self-report measures of exposures to neurotoxicants while in the Gulf region. PCI contact information and interview data (conducted in 1997-1998) were provided to the Principal Investigator by Dr. Michael Kilpatrick, M.D., Deputy Director of the Deployment Health Support Directorate (previously known as OSAGWI) through their System of Records Notice which permits release of records to the Veterans Administration. The DHSD released the records to the VA Boston Healthcare System through a Memorandum of Understanding (MOU). The MOU provided assurances from the VA Boston Healthcare System and the Boston Environmental Hazards Center (a joint program of the VA Boston Healthcare System and Boston University).

The MOU states:

1) The released PCI records will only be used for the purposes of the current study

2) Only study personnel will have access to the released records

3) The released information will be safeguard to preserve the confidentiality of the data

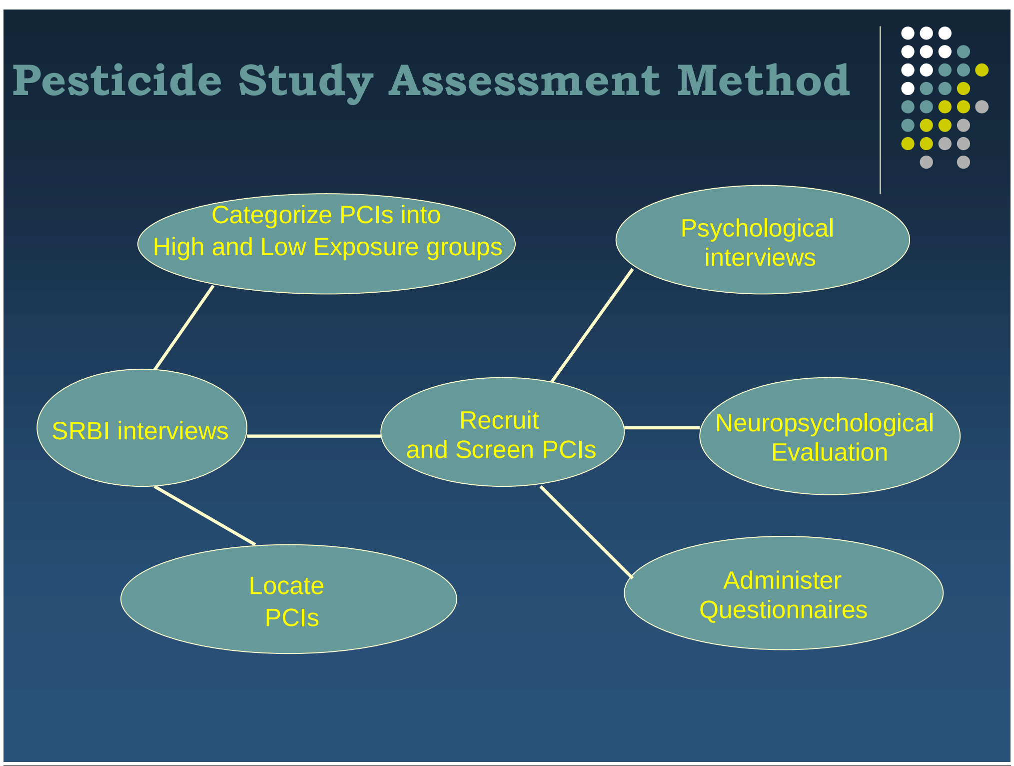
4) Any personal identifiers will be removed from any interim and final reports that are prepared as a consequence of this study.

The PCI interview records were used in conjunction with current interview data to categorize individuals into high and low pesticide and PB (pyridostigmine bromide) exposure categories. In addition, these interviews have also been used in conjunction with the current exposure questionnaires to perform dose-estimates for pesticides and PB. Mr. William Bradford, lead author of the Pesticides Environmental Exposure Report, will continue to assist with these dose-estimates in year 4.

Task 1 b. SRBI, an independent contracting company will contact PCIs and obtain current address and administer a brief follow-up questionnaire.

An outside research firm (Schulman, Ronca, & Bucuvalas, Inc., SRBI) with extensive experience collecting data from veterans of the U.S. Armed Forces was subcontracted to obtain current telephone numbers and addresses for the PCIs and to administer a brief follow-up questionnaire by telephone. The recruitment process was as follows: PCIs were sent a letter from the PI explaining that SRBI would be contacting them to conduct a brief telephone interview and obtain their current contact information for the study. A postage paid opt-out postcard was included with this introduction letter. If the PCI elected to return this postcard, there was no further contact with this individual for the study. If a postcard was not returned to the study staff, SRBI attempted to contact the PCI and determine if they wished to participate in the brief interview regarding their pesticide and PB exposures during the Gulf War. Ten individuals returned the opt-out postcards and were not contacted further for this study. From the remaining list, SRBI was successful in completing 160 telephone interviews with PCIs regarding neurotoxicant exposures resulting in a live refusal rate of just seven percent. SRBI was also able to find current contact information for all 293 PCIs and identify that one PCI was deceased. The study design is presented in the figure below followed by tables of demographic information computed from the SRBI telephone interview data.

Figure 1. Pesticide Study Assessment Design



From the SRBI telephone interviews, demographic and exposure data was collected from each responding PCI. The demographic information is reported in table 1. From this group of 160 study respondents, 140 were male and 20 were female. The average age for the group of Gulf War veterans was 48 years old and the group was largely Caucasian (85%). The most commonly reported current health problems reported by these study participants were hypertension, cardiovascular disease, arthritis, asthma, back and joint pain, skin rash and memory problems. When broken down into groups based on high and low groups for pesticides and PB, the only notable differences were found in increased reporting of hypertension (12 vs. 6 PCIs), cardiovascular disease (6 vs. 2 PCIs) and arthritis (6 vs. 1 PCI) in the high pesticide group compared with the low pesticide group. While the high and low PB groups did not appear to differ very much with respect to health symptom reporting from this brief health query included in the telephone interviews. The larger study questionnaire with more in-depth questions regarding medical diagnoses will help to better characterize these groups in terms of health outcomes and show their significance. The demographic breakdown of the SRBI surveys is reported in table 1.

Table 1. Demographic Breakdown for SRBI Survey Respondents		
Gender	Frequency	Percent
Male	140	87.5
Female	20	12.5
Total	160	100

Current Age for SRBI Survey Respondents		
Minimum	Maximum	Mean
33	74	48

Ethnicity for SRBI Survey Respondents		
Ethnicity	Frequency	Percent
African American	12	7.5
Asian American	3	1.9
Caucasian	136	85.0
Hispanic American	6	3.8
Other	3	1.9

Health Symptom Self-report for SRBI Respondents		
Symptom	Frequency	Percent
Hypertension	23	14
Cardiovascular Disease	11	7
Arthritis	12	8
Asthma	10	6
Back Pain	11	7
Joint Pain	13	8
Skin Rash	14	9
Memory Problems	14	9

Task 1 c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure.

Pesticides were used widely in the Gulf War to protect troops from such pests as sand flies, mosquitoes and fleas that can carry the infectious diseases leishmaniasis, sand fly fever and malaria. Indeed, of the nearly 700,000 US troops deployed to the Gulf region, only 40 cases of infectious diseases were documented (Winkenwerder Jr, W., 2003). US forces used pesticides in areas where they worked, slept, and ate throughout the GW. In fact, on any given day during their deployment, GW veterans could have been exposed to 15 pesticide products with 12 different active ingredients and pesticide applicators were likely exposed to more pesticide products and at higher doses. Troops used pesticides for a number of reasons, including personal use on the skin and uniforms as an insect repellent, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, and as delousing agents applied to enemy prisoners of war. These widespread, commonly reported uses supported the decision by the OSAGWI to investigate pesticide exposures as a potential contributor to unexplained illnesses in GW veterans. According to the OSAGWI report, the pesticides of potential concern (POPCs) used by US military personnel during the GW can be divided into five major classes or categories: 1) organophosphorus pesticides (OP), such as malathion and chlorpyrifos; 2) carbamate pesticides, such as bendiocarb; 3) the organochlorine, lindane; 4) pyrethroid pesticides, such as permethrin; and 5) the insect repellent DEET (see figures 2 through 4). A recent review of thousands of pesticides as part of the Food Quality Protection Act by the Environmental Protection Agency (EPA) has resulted in the re-evaluation of the safety of some OP pesticides resulting in the restricted use or banning of several of the most commonly used chemicals including chlorpyrifos, diazinon and malathion. As part of this sweeping pesticide review, the EPA also suggested that some OP pesticides may have endocrine disrupting properties. For example, malathion was reported to affect thyroid functioning and to be associated with thyroid tumors in this report (www.epa.gov/pesticides/cumulative/rra-op).

Figure 2. Pesticide use and Application Overview.

Pesticide Use and Application Overview

Use	Designation	Purpose	POPCs, Active Ingredient	Application Method	User or Applicator
General Use Pesticides	Repellents	Repel flies and mosquitoes	DEET 33% cream/stick	By hand to skin	Individuals
			DEET 75% Liquid	By hand to skin, uniforms or netting	
			Permethrin 0.5% (P) Spray	Sprayed on uniforms	
	Area Spray	Knock down spray, kill files and mosquitoes	d-Phenothrin 0.2% (P) Aerosol	Sprayed in area	
	Fly Baits	Attract and kill flies	Methomyl 1% (C) Crystals	Placed in pans outside of latrines, sleeping tents	Individuals, Field Sanitation Teams, Certified Applicators
			Azamethiphos 1% (OP) Crystals		
	Pest Strip	Attract and kill mosquitoes	Dichlorvos 20% (OP) Pest Strip	Hung in sleeping tents, working areas, dumpsters	
Field Use Pesticides	Sprayed Liquids (emulsifiable concentrates, ECs)	Kill flies, mosquitoes, crawling insects	Chlorpyrifos 45% (OP) Liquid	Sprayed in corners, cracks, crevices	Field Sanitation Teams or Certified Applicators
			Diazinon 48% (OP) Liquid	Sprayed in corners, cracks, crevices	Certified Applicators
			Malathion 57% (OP) Liquid		
			Propoxur 14.7% (C) Liquid		
	Sprayed Powder (wettable powder, WP)	Kill flies, mosquitoes, crawling insects	Bendiocarb 76% (C) Solid		
	Fogs (Ultra-Low Volume Fogs, ULVs)	Kill flies, mosquitoes	Chlorpyrifos 19% (OP) Liquid	Large area fogging	Certified Applicators
			Malathion 91% (OP) Liquid		
Delousing Pesticide	Delousing Pesticide	Kill lice	Lindane 1% (OC) Powder	Dusted on EPWs, also available for personal use	Certified Applicators, Military Police, Medical Personnel

Figure 3. Active ingredients in pesticides of potential concern.

Active ingredients contained in pesticides of potential concern

Repellents	Pyrethroids	Organophosphates	Carbamates	Organochlorines
DEET	Permethrin	Azamethiphos	Methomyl	Lindane
	D-Phenothrin	Chlorpyrifos	Propoxur	
		Diazinon	Bendiocarb	
		Dichlorvos		
		Malathion		

Figure 4. Applicator exposure levels reaching levels of concern

Applicator personnel additional exposures which exceeded the levels of concern

Pesticide	Active Ingredient/Class	Exposure Scenario
Sprayed liquids	Chlorpyrifos (OP)	High
	Diazinon (OP)	Medium, High
	Malathion (OP)	High
Sprayed powders	Bendiocarb (C)	Low, Medium, High
Fogs	Chlorpyrifos (OP)	High
	Malathion (OP)	High
Delousing	Lindane (OC)	Medium, High

OP = Organophosphate
C = Carbamate
OC = Organochlorine
*Lindane use also may increase the risk of cancer

Guidelines for pesticide and PB exposure are presented in the tables 2 and 3 and were used to classify participants into high and low exposure categories based on prior OSAGWI interviews and current interviews conducted by SRBI.

Table 2. Guidelines for Pesticides

Low exposure

An individual is assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below. For example, an individual exposed to pyrethroids other than via fogs, but no other pesticides, would be assigned to a low pesticide exposure group.

High exposure

An individual is assigned to the high-exposure category for pesticides if any of the following apply:

1) PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, other than minor skin irritation, at least once. A general statement, such as "became ill" will qualify.

2) PCI probably applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits ($\geq$2 pounds handled), and/or fogs. PCI may or may not have worn adequate personal protective equipment (PPE).

3) PCI was probably present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.

4) PCI probably spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.

5) PCI probably applied DEET to self at least 30 times. PCI must provide enough information to conclude that usage was equivalent to or above this level. DEET application 30 times per month is the 25th percentile value determined by the RAND (2000) survey for ground forces who used DEET (50% reported no use).

Table 3. Guidelines for PB

Low exposure

An individual is assigned to the low-exposure category for PB if no acute signs and/or symptoms of exposure were reported *and* any of the following apply:

1) The individual reported not using PB.

2) The total dose reported was less than or equal to 180 mg PB active ingredient.

3) The individual reported using PB, but could not recall sufficient details to conclude that the dose was probably greater than 180 mg PB active ingredient.

High exposure

Individuals are assigned to the high-exposure category for PB if either of the following apply:

1) The total dose was probably greater than 180 mg PB active ingredient.

2) The individual reported taking any PB and also reported experiencing acute signs and/or symptoms of exposure.

PB and pesticide exposure were categorized as high and low based on the previous OSAGWI interviews and the current SRBI interviews. From these interviews, 97 PCIs were categorized in the high pesticide exposure group and 63 PCIs were categorized in the low pesticide exposure group and 81 PCIs were categorized in the high PB group and 79 PCIs were categorized in the low PB group. Additional categorization for pesticide and PB exposure and Khamisiyah notification (identifying those potentially exposed to chemical weapons) are listed in table 4.

Table 4. PB and Pesticide Exposure Categories

Self-reported PB Exposure during the Gulf War		
	Frequency	**Percent**
Yes	**118**	**74**
No	**33**	**20**
Don't Know	**9**	**6**
Total	**160**	**100**
Self-reported Pesticide Exposure during the Gulf War		
	Frequency	**Percent**
Yes	**122**	**76**
No	**30**	**19**
Don't Know	**8**	**5**
Total	**160**	**100**
Exposure Categories for PB and Pesticides		
	PB	**Pesticides**
Low	**79**	**63**
High	**81**	**97**
Total	**160**	**160**
Khamisiyah Weapons Depot Notification		
	Frequency	**Percent**
Yes	**59**	**37**
No	**101**	**63**
Total	**160**	**100**

Task 1 d. Identify pool of potential subjects for each of four exposure categories to recruit.

Combining the previously described high and low exposure groups for the pesticide and PB groups allowed for four category groupings (table 5). The categories include high pesticide and high PB exposure, high pesticide and low PB, low pesticide and high PB, and low pesticide and low PB. The goal of the study was to recruit 40 study participants from each of the four exposure categories with the study participants sequentially assigned to one of the four study groups based on exposure combination. However, the high pesticide/low PB (n =37) and the low pesticide/high PB (n = 20) groups appear to be smaller than expectation and may not allow for such large groupings (table 5). However, analyses controlling for different exposure groups will be employed to control for different group sizes if necessary.

Table 5. Four Exposure Categories for PB and Pesticides

	Pesticide categories		
PB categories	**Low**	**High**	**Total**
Low	**42**	**37**	**79**
High	**20**	**61**	**81**
Total	**62**	**98**	**160**

Task 1 e. Screen potential subjects for exclusion criteria.

The exclusion criteria for this study include current substance abuse, substantial traumatic brain injury or other documented neurological illness precluding the use of a computer. Prior substance abuse and current medications are recorded but do not constitute exclusion criteria.

These exclusion criteria were chosen so that study participants who may perform poorly on cognitive testing for known reasons other than environmental exposures could be screened out to prevent potential study confounders.

From the SRBI telephone interviews, a review of reported health symptoms was performed and no participant from these interviews reported significant head injury or other significant neurological illness that might interfere with performing the cognitive and computer testing parts of the study protocol. There was one case who reported a history of an acoustic neuroma recently removed, one case of multiple sclerosis (MS) and two cases of mini-stroke or transient ischemic attack (TIA). However, all of these study participants were able to complete the entire study protocol. In the 28 recruitment trips conducted to date, none of the study participants were screened out based on these criterion.

Subject recruitment is ongoing and PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain a serious brain injury. Screening for exclusion criteria occurs during the telephone recruitment phase of the study and will be ongoing during the study recruitment efforts.

Task 2a. Recruitment of 61 study subjects and arrange for travel to multiple study sites.

Sixty participants were recruited during year 3 and completed the study protocol (cognitive evaluation, psychological interviews and exposure questionnaires). This group included 52 men and 6 women including 5 active duty personnel and 55 veterans. Combined with the years 1 & 2 recruitment totals of 12 and 47 study participants, a total of 119 study participants have been recruited to date. Subject recruitment efforts are presented in the table below. Seven additional subjects were interested in participating in our study but either had schedule conflicts during our recruitment trip to their area (n = 1), became unexpectedly ill and had to cancel their appointment with us (n = 2) or cancelled for no stated reason (n = 4).

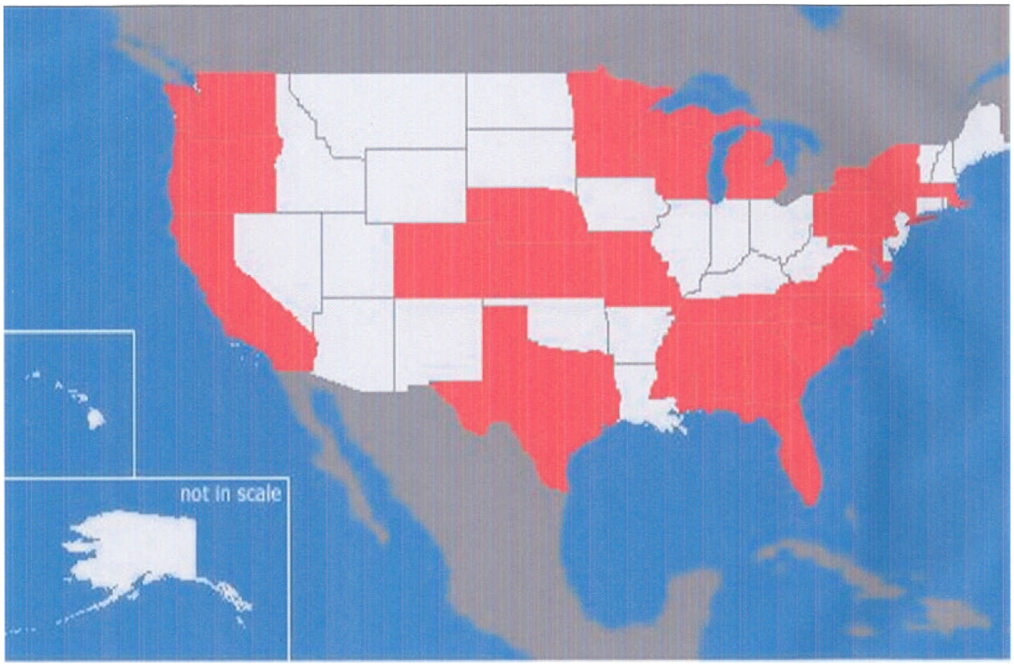
Table 6. Subject Recruitment Efforts for Years 1 -3

Study Year	**Frequency**	**Projected**	**Percent**
Year 1	**12**	**20**	**60%**
Year 2	**47**	**50**	**94%**
Year 3	**60**	**50**	**110%**
Total recruitment	**119**	**120**	**99%**

During year 3, recruitment trips were conducted in Washington State, North Carolina, South Carolina, Wisconsin, Colorado, Nebraska, Kansas, Oregon, California, Florida, Michigan, Alabama, Mississippi, Virginia and Georgia. In total, 120 study subjects were originally projected to be recruited for Years 1-3, and a 99 percent recruitment rate was achieved for total recruitment with only eight individuals declining to participate. These recruitment trips were successful with only seven cancellations of scheduled participants.

See figure 2 below for a map of states visited for recruitment efforts to date.

figure 2. Recruitment trips for years 1- 3.



Although the current address for each PCI was obtained by SRBI during their telephone interviews, we have found that many of the PCIs are quite mobile and have moved to different states from their previous SRBI interview residence. However, using internet and telephone searches and interagency agreements for address searches, we were able to find correct addresses for most of the potential study participants. In addition, five of the active duty personnel had been deployed oversees or activated domestically to aid in hurricane relief and were subsequently not able to participate in the study during year 2 of the study. We were however able to recruit 5 additional active duty personnel to participate in the study during year 3 for a total of 8 active duty study participants (out of 14 total). The recruitment strategy will continue to target the more populated areas first in order to make the most use of travel funds and will likely include revisiting states that were previously visited due to PCIs moving from one state to another during the time of the study. The next planned recruitment trips will include Texas, New Mexico, Florida, Arkansas, Missouri, Georgia, North Carolina and Tennessee. We also plan to continue to use internet and other available telephone searches to obtain current residences for participants who may have recently moved. It is anticipated that the recruitment of 41 additional study participants (40 projected for Year 4 plus 1 from Year 3 projections) will be obtainable by the end of Year 4 for a final total of 160 recruited study participants. Given the favorable response from the first three years of recruitment efforts, significant difficulties with subject recruitment are not anticipated at this time although additional smaller recruitment trips will likely be necessary to achieve this final recruitment goal for year 4.

The exposure classifications are presented below and include 83 high pesticide, 36 low pesticide, and 68 high PB, 51 low PB categories.

Table 7. Exposure Classifications for First 119 Study Participants

	Pesticide Categories		
PB categories	**Low**	**High**	**Total**
Low	**18**	**33**	**51**
High	**18**	**50**	**68**
Total	**36**	**83**	**119**

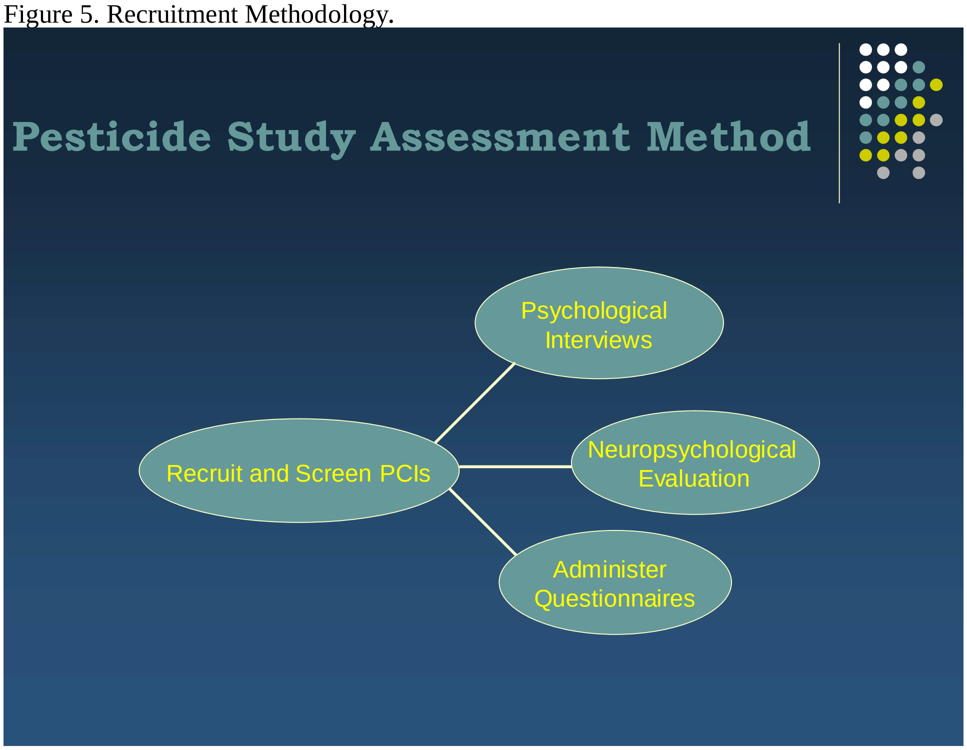
Table 8. PCI Current Residence by State

AL	4	MS	3
AR	6	MT	1
AZ	3	NC	15
CA	7	NE	3
CO	7	NH	1
CT	1	NJ	1
DC	1	NM	5
DE	1	NV	2
FL	22	NY	5
GA	15	OH	2
HI	2	OK	3
IA	1	OR	1
IL	4	PA	12
IN	3	SC	4
KS	4	TN	16
KY	3	TX	24
LA	1	UT	1
MA	1	VA	12
MI	8	WA	14
MN	10	WI	10
MO	22	Active Duty	14

<u>Recruitment Methodology</u>

When recruiting study participants, the PI or study staff contact PCIs participating in the SRBI interviews to describe the study and establish whether the PCI will participate in the cognitive evaluation. The initial contact with the study staff consists of a description of the study, describing the types of assessment, time required, and reimbursement for their time and effort. Subjects have an opportunity to ask questions about the procedure. They are informed that whether or not they participate will have no bearing on their medical care and that, if they choose to participate, they may withdraw at any time without prejudice. They are asked to indicate whether they wish to participate, wish not to participate, or wish to defer this decision. In the latter case they are asked whether we may contact them again to determine their decision. Gulf War veterans who are currently on active duty are contacted at home in the evening hours and will not be contacted during duty hours. Active duty PCIs are not compensated for their participation as there are restrictions on compensation to active duty personnel. PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for alcohol or other substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain serious brain injury). Prior substance abuse and current medications are recorded but do not constitute exclusion criteria. An appointment during one of the field trips is scheduled for subjects agreeing to participate. PCI veterans retained in the study sample are presented the study consent form for signature. The study methodology is presented in figure 5.

Figure 5. Recruitment Methodology.



Task 2b. Perform cognitive evaluations and psychodiagnostic interviews with 61 participants

The goal for year 3 was to recruit and perform cognitive and psychodiagnostic interviews with 61 study participants. As described above, a total of 60 study participants were recruited in year 3 catching up with minor recruitment difficulties in year 2. In addition, all 60 of the study participants completed the entire study protocol and did not express any difficulties with the length of the examination. The cognitive evaluations were completed in 1.5 hours for most of the study participants and the psychodiagnostic interviews required an additional twenty minutes in most cases to complete. Study participants are able to take breaks during the study protocol session if they feel they need them and can fill out their questionnaires and mail them back if necessary. With this strategy, it is not anticipated that there will be much missing data from the study protocols. However when missing data is encountered during data analysis, interpretative statistics will be employed whenever possible.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in tables 9 and 10 followed by a description of the study instruments and procedures.

Table 9. Definitions of Neuropsychological Domains

I. <u>General Intelligence:</u> IQ scores in all domains or in a specific domain (verbal or visual-motor); academic skills; performance on tests of reading, spelling, arithmetic, vocabulary, academic knowledge.
II. <u>Attention, Executive System:</u> Capacity to focus on incoming stimuli; includes vigilance, tracking and capacity to divide attention between competing stimuli.
III. <u>Motor:</u> Speed and dexterity in completing tasks.
IV. <u>Visuospatial function:</u> Processing of nonverbal information such as visual designs, visual constructions, and geographic information; includes sequencing, organization (mental) and constructional ability.
V. <u>Memory:</u> Anterograde memory function involves encoding, storing, retrieving and retaining new information. Retrograde memory function refers to ability to recall information learned in the past.
VI. <u>Mood/Personality:</u> Includes temporary and characterologic mood states and characterologic personality traits or tendencies.
VII. <u>Motivation and Malingering:</u> An evaluation of effort.

Table 10. Full Neuropsychological Test Battery.		
TEST NAME	**DESCRIPTION**	**OUTCOME MEASURE**
I. Tests of Premorbid Functioning		
Wechsler Adult Intelligence Scale-Revised (WAIS-III; Wechsler, 1997) Information subtest	Information usually learned in school; to assess native intellectual abilities	Raw Score
Boston Naming Test (BNT; Kaplan et al., 1983)	Confrontation naming of line drawings; to assess verbal abilities	Raw Score
II. Tests of Attention, Vigilance and tracking		
Trail-making Test (Reitan &Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)	Completion
Computerized Continuous Performance Test (CPT; Letz & Baker, 1988)	Target letter embedded in series of distractors; to assess sustained attention and reaction time	Reaction Time Total Errors
Wisconsin Card Sorting Test (WCST; Heaton et al, 1993)	Requires use of feedback to infer decision making rules; assesses problem solving ability and flexibility	Total # Sorts
III. Tests of Motor Function		
Finger Tapping Test (FTT; Letz and Baker, 1988)	Speed of tapping with index finger of each hand; assesses simple motor speed	Mean Taps
Grooved Pegboard Test (Klove, 1963)	Speed of inserting pegs into slots using each hand separately; assesses motor coordination and speed	Raw Score
IV. Tests of Visuospatial Function		
Hooper Visual Organization Test (HVOT; Hooper, 1958)	Identifying objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli	Raw Score
Rey-Osterreith Complex Figure (ROCFT; Corwin & Blysma, 1993)	Copying a complex geometric design; assess ability to organize and construct	Raw Score

TEST NAME	DESCRIPTION	OUTCOME MEASURE
V. Tests of Memory		
California Verbal Learning Test (CVLT II; Delis et al., 1987)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies	Total Trials 1-5 Long Delay
ROCFT-Immediate and 20 minute recall	Immediate and Delayed recall of a Complex figure	Raw Score
Stanford-Binet Copying Test (Terman & Merrill, 1973)	Immediate and 10 minute delay of 16 designs	Raw Score
VI. Tests of Personality and Mood		
Profile of Mood States (POMS; McNair et al., 1971)	65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales	T-Scores
VII. Tests of Motivation		
Test of Motivation and Malingering (TOMM; Tombaugh, 1996)	Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering	Raw Score

Assessment Instruments and Procedures

1. Cognitive Assessment.

A tester who is blind to the exposure status of the subject administers the neuropsychological test battery. The neuropsychological test battery assesses the functional domains of general intelligence, attention, executive abilities, motor function, visuospatial skills, memory, and mood (table 9). The battery is described in detail in Table 10. It includes 1) tests designed to tap relatively stable native intellectual abilities including the Information subtest from the WAIS-III, and the Boston Naming Test. On these tests, it is expected that the scores will be consistent with estimated native IQ based on age, education, and occupational history and 2) tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions that have in past studies demonstrated utility in the assessment of toxicant-induced brain damage, and psychiatric disorders. The domains included in this category are attention and executive function, motor skills, mood and memory.

Sustained attention is measured by number of errors on a test of continuous performance (CPT), a computer-assisted test from the Neurobehavioral Evaluation System (NES), an instrument widely used in the field of occupational health, that represent adaptations of traditional neuropsychological instruments for computerized stimulus presentation and recording of responses. The NES instruments have reliable psychometric properties and have demonstrated validity in epidemiological and laboratory studies of exposure to a wide variety of neurotoxicants. Also used as measures of executive functioning, are measures of cognitive flexibility (Wisconsin Card Sort test) and alternation of set (Trail making test, part B).

Motor functioning is measured by the mean of five trials on each hand on the finger tap test, the time to completion on the grooved pegboard test and reaction time on the CPT test.

Previous studies of occupational pesticide exposure have documented changes in reaction time and motor speed (NCTB). Therefore, we predict decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures.

The test battery also includes the Profile of Mood states as a self-report assessment of current mood. The indicators of importance are current fatigue, confusion, tension and depression. Mood has been shown to be associated with changes in subcortical-limbic system and neurotransmitters as a result of toxicant exposures and as such, mood will be treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we administer the Rey-Osterrieth Complex Figure Test and document total scores for the copying subtest (rey-osterrieth scoring out of 36). In addition, a qualitative scoring system is also used to assess approach to the task and specific types of errors committed. We expect that individuals with increased exposures will have difficulty maintaining the overall configuration, tremulous writing and segmentation as a result of basal ganglia dysfunction commonly seen in these people. In addition, the Stanford Binet copying task will be used in this test battery to document further impairment in visuoconstruction as has been found in our prior research. The total score for copying (out of 16 possible) is expected to be diminished in those who have significant neurotoxicant exposures. In addition, we will also compare total number of errors (out of 120 possible) as well as type of errors as discussed above.

Individuals who have documented exposures to neurotoxicants have had difficulty in the areas of acquisition and retrieval. Therefore, we will be examining verbal and nonverbal memory with the use of the Rey-Osterrieth Complex Figure Immediate and Delayed recall and the CVLT-II measures of total recall trials 1 to 5 (raw score) and Long-delay free recall (raw Score).

Lastly, a measure of response consistency will be used to document the possibility of diminishment in motivation. Raw scores (out of a possible score of 50) will be computed and we expect that only a few individuals will fall below a score of 45 (indicating decreased motivation).

In the event of decreased motivation scores on this test, analyses will be performed with and without these individual's test scores to assess for potential differences. If there are significant differences between the groups, then the group with low motivational scores will be removed from the dataset.

Because this study compares neuropsychological functioning in pesticide-exposed individuals many years after their GW exposures, the question arises how does one decide if decreased performance in cognitive functioning is actually associated with pesticide exposure or if those individuals with cognitive deficits simply report more pesticide exposure. One way to examine this problem with self-reported exposures and correlating them with current brain functioning is by comparing <u>patterns</u> of cognitive performance in relation to the reported exposure. The field of behavioral neurotoxicology is an established field that studies the effect of brain/behavior (test performance) relationships and specific types of neurotoxicant exposures.

Epidemiological studies during the past 30 years have examined the impact of exposure to metals (e.g., lead, mercury, arsenic), organic solvents (e.g., trichloroethylene, n-hexane, petroleum distillates), and pesticides (e.g., organophosphates, carbamates) on brain functioning and found different cognitive patterns with these exposures. For example, studies of solvent exposure have reliably shown disturbances in executive function, attention, visuospatial skills, short-term memory, and mood (Anger, 1990, White et al., 1992 and Echeverria & White, 1992) Studies of lead-exposed workers have yielded similar findings along with decrements in verbal reasoning and motor functions (Baker et al., 1984, Hanninen et al., 1978 and Yokoyama et al., 1988). While studies of pesticide-exposed agricultural workers have shown disturbances in processing speed and mood and sequelae from overt poisoning from organophosphate pesticides can result in lasting deficits in the domains of visuomotor, attention/executive functioning, motor functioning and mood. Therefore, we would be comparing not only specific test performance to self-report of pesticide exposure but also the <u>pattern</u> of cognitive performance in the domains of attention/executive functioning, memory, visuospatial skills, motor skills and mood.

In addition to exposure class, other factors (e.g., age, education, intelligence, prior exposures, medical and health concerns, alcohol abuse, life stress, and workplace stress) are likely to influence performance on cognitive tests (Grasso et al., 1984, Hanninen, 1988, Proctor et al, 1996 and Letz, 1993.) and must be taken into account in evaluating the effects of exposure to known or suspected toxicants. Therefore, the study was designed to be able to compare cognitive patterns on five different domains in individuals reporting higher and lower pesticide exposures (table 9).

We have made specific hypotheses of how the higher pesticide exposed individuals will perform based on prior epidemiological studies showing the cognitive pattern of motor (performance speed) and mood decrements in pesticide exposed individuals. We have also included a series of questionnaires to the study protocol that will obtain demographic (age, education, gender, premorbid intelligence) and diagnostic variables (Post-Traumatic Stress Disorder, Major Depression etc.) that could affect cognitive performance and should be controlled for in any analyses comparing self-reported exposures to neurotoxicants. In addition, an exposure questionnaire is also included in the study protocol (SNAC) that queries for other types of neurotoxicant exposures that could affect cognitive performance (exposures from hobbies and post-military employment) that will also be used as control variables.

2. Psychological Assessment.

1) Subjects are administered the Structured Clinical Interview for DSM-IV (SCID) and a current Global Assessment of Functioning score is assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major

Axis I disorders. Dr. Krengel who will also be blind to the exposure data administers the Clinician Administered PTSD Scale IV (CAPS), a state-of-the-art instrument for confirming the diagnosis of current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties. Subjects fill out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PTSD checklist), and to identify traumatic events, military or civilian (Modified Life Events Checklist, Traumatic Events) (table 11).

2) Dr. Krengel also conducts a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Subjects are asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors.

Treatment of Data

The aims of this study are to determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans, to determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans, and to assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

We will examine the relationship between neurotoxicant exposure and neuropsychological performance through multivariate multiple regression. This will include indicator variables to account for group status (1 = High PB, High Pesticide, 2 = High PB, low Pesticide, 3 = Low Pesticide, High PB, 4 = low Pesticide, Low PB) as well as individual risk factors and intervening risk factors that might be related to outcomes. Additional analyses exploring the interactions between the exposures and neuropsychological outcome will be pursued. We will look at the relationship of stress and health symptoms through the multiple regression analyses as described above. Steps have been employed to minimize missing data including offering breaks during cognitive testing, allowing participants to complete questionnaires at home and mailing them back and completing psychological interviews by telephone (when necessary due to time constraints or fatigue of study participants). However when data is not obtainable, the missing data will be interpolated statistically whenever possible by comparing means of similarly answered questions.

Task 2c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 61 study subjects by study questionnaires.

All sixty study participants recruited in year 3 completed the study questionnaire. The study questionnaire is comprised of several health and mental health scales. These include: the health symptom checklist, Brief Symptom Inventory (BSI), PTSD checklist (PCL), Modified Life Events Checklist (Traumatic events), Veterans Version of the SF12 (SF12V), and the pesticide exposure questionnaire (SRBI questionnaire). See Table 11 for questionnaire descriptions and Table 12 for frequencies of psychiatric diagnoses, medical conditions and health symptom reports for the first 119 study participants. In general, psychiatric diagnoses were relatively high for PTSD (10%) and depression (9%) when measured by a structured clinical interview. The most common medical diagnoses reported in the study sample included allergies, hypertension, arthritis, deafness, asthma, cancer, neurological diseases and irritable bowel syndrome. In depth health symptom questions from the health symptom checklist (HSC) in the study questionnaire (see table 11) showed elevated rates in joint pain (79%), sleep difficulties (73%), muscle pain (63%), word finding problems (58%), concentrating difficulties (51%), weakness (50%) and forgetfulness (50%). These same health symptoms were the most commonly reported in our prior studies and clinical evaluations of treatment-seeking Gulf War veterans from the New England area with the exception of weakness (Sullivan et al., 2003). When comparing health symptoms and medical diagnoses by pesticide exposure, all diagnoses were higher in the high pesticide exposed group, (diabetes 6 vs. 2; heart attack 3 vs. 0; arthritis 26 vs. 7, lung disease 8 vs. 1, chronic rash 21 vs. 3; high blood pressure 27 vs. 10) but no significant differences were found. Complete analyses between exposure groups will be done when a larger study sample is recruited and higher statistical power is attained.

Table 11. **Study Questionnaire Descriptions**

Name	**Description**
Demographics	Subjects report information on age, education, gender, ethnicity, marital status, GW duty service (active vs. reserve/National Guard), military rank and current military status.
SF12V	Veterans version of the SF12 which compares functional health-related quality of life. It includes a physical component score and a mental component score.
Health Symptom Checklist (HSC)	A comprehensive list of 34 frequently reported health and mental health symptoms. The HSC determines how often in the past 30 days the health symptoms were experienced. Symptoms from nine body systems are assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological).
Medical Conditions	Included in this checklist is a list of 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it was diagnosed.
Brief Symptom Inventory (BSI)	The Global Severity index of the BSI is a summary index that represents the most sensitive single inventory indicator of a subjects' psychological distress level by combining information on a number of psychological symptoms and their intensity.
PTSD checklist (PCL)	A 17-item checklist following DSMIII-R or DSM-IV guidelines and is a structured interview for clinical diagnosis of PTSD.
Modified Life events checklist (Traumatic Events)	Modified version of the life events checklist to check for traumatic life events.
Structural Neurotoxicant Assessment Checklist (SNAC)	The SNAC assesses the degree of past exposure to neurotoxicants during civilian and military occupations includes questions pertaining to recent occupational and environmental exposures. Questions include length stay, geographical location, and environmental exposure during deployment (type, intensity, frequency, duration, locale).
Pesticide Exposure Questionnaire (SRBI brief questionnaire)	This telephone interview was conducted by SRBI to obtain pesticide and PB exposure estimates. Questions include what pesticides were used during the Gulf War and what most pressing health problems that the respondent currently reports.
Telephone Recruitment form	This telephone recruitment form is used by study staff to recruit and track responses for potential study participants. Questions include current medical diagnoses, medication use, and participation in other Gulf War related studies.

Table 12. Psychiatric Diagnosis and Health Symptom Report in first 119 Participants

Interview Diagnosis	Frequency	Percent
PTSD	12	10
Major Depression	11	9
Multiple Chemical Sensitivity	1	1
Chronic Fatigue Syndrome	2	2
Medical Conditions		
Hypertension	37	31
Asthma	13	11
Heart Attack	3	3
Diabetes	8	7
Multiple Sclerosis	1	2
Other Neurological Disease	11	9
Cancer	13	11
Stroke/cerebrovascular disease	4	3
Allergies	34	34
Arthritis	33	28
Irritable Bowel Syndrome	10	9
Thyroid disorder	8	7
Tumors or growths	5	4
Neuropathy	3	3
Lung Disease	9	8
Deafness	17	14

Health Symptoms		
Joint Pain	**86**	**79**
Skin Rash	**36**	**35**
Sleep Trouble	**80**	**73**
Diarrhea	**48**	**44**
Upset stomach	**50**	**47**
Difficulty Concentrating	**30**	**51**
Confusion	**39**	**36**
Forgetfulness	**57**	**50**
Muscle pain	**68**	**63**
Weakness	**53**	**50**
Word finding problems	**62**	**58**

Task 3a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing.

Interview findings, neuropsychological assessment results, and questionnaire data for each of the 119 completed study participants have been scanned into a dataset by using teleform software and cleaned through quality control measures. SPSS datasets have been created to analyze the data obtained. This procedure will be ongoing as subject recruitment continues.

Task 3b. Interim statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically.

Analyses of the first 110 subjects were performed and presented at the International Neuropsychological Society annual meeting in Portland, OR in February 2007. Multivariate analysis of variance was computed to compare high and low pesticide exposures on neuropsychological measures including the domains of attention/executive system, language, motor, visuospatial and memory. The results are presented in table 12. Overall, the results suggested a significant effect of high pesticide exposure and lowered mean reaction times on the continuous performance test, differences in executive functioning on the Wisconsin card sort test and visual memory differences on the Rey-Osterrieth complex figure. When interaction effects of pesticides, PB and Khamisiyah notification were compared using multivariate analyses, an interaction effect was found for lower visuointegration skills (Hooper test $p = .002$).

When health symptom patterns were compared in a separate analysis using chi-square analyses, PCIs with high pesticide exposure reported significantly more difficulties with gastrointestinal difficulties, skin rash, muscle weakness, confusion and word-finding difficulties as measured by the 34 item health symptom checklist (see table 13). Other reported medical diagnoses were not significantly different in the high and low pesticide or PB groups. However, analysis comparing medical diagnoses with Khamisiyah notification (and potential low-level nerve agent exposure) was significantly associated with irritable bowel syndrome in the notified group (20% of Khamisiyah group, $p = .005$). As additional subjects are recruited and statistical power is improved, regression analyses of the four groupings will be performed as described in the treatment of data section.

Table 13. Preliminary health symptom results in first 110 study participants.

Health Symptom	Pesticide High Exposed % reporting n=77	Pesticide Low Exposed % reporting n=33	Chi-Square X^2 (p-value)	Odds Ratio OR (p-value)
Diarrhea	81	19	5.7 (.017)	2.8 (1.1-7.0)
Upset Stomach	84	16	9.6 (.002)	4.1 (1.6-10.2)
Skin Rash	83	17	5.3 (.021)	3.1 (1.2-8.6)
Weakness	83	17	8.4 (.004)	3.6 (1.5-8.9)
Muscle Pain	78	22	6.2 (.012)	2.8 (1.2-6.7)
Confusion	82	18	4.7 (.029)	2.8 (1.0-7.3)
Word Finding Difficulty	82	18	10.4 (.001)	4.1 (1.6-9.7)
Sleep Problems	75	25	3.5 (.062)	2.3 (.95-5.5)

Table 14. Neuropsychological Functioning in high and low pesticide exposed groups

Cognitive Domain	High Pesticide Group Mean (sd) n = 77	Low Pesticide Group Mean (sd) n = 33	Significance P-value
Attention/Executive			
Trails A – time to completion	32.9 (13.8)	28.1 (7.9)	.235
Trails B – time to completion	73.3 (42.0)	65.1 (20.6)	.757
WCST – number of sorts	3.6 (1.2)	4.0 (1.3)	.040
CPT – # false positives	1.6 (2.1)	2.1 (2.4)	.219
CPT - # no responses	.8 (2.4)	.1 (.3)	.572
Language			
Boston Naming – total correct	57.1 (2.4)	57.3 (2.9)	.939
Psychomotor			
Finger Tap test – latency of response, preferred hand	180.5 (35.5)	172.9 (25.2)	.970
Finger Tap test – latency of response, non-preferred hand	192.3 (43.5)	181.7 (44.3)	.451
Finger Tap test - # taps preferred hand	54.2 (9.8)	55.2 (54.2)	.830
Finger Tap test - # taps non-preferred hand	51.7 (7.8)	53.5 (8.7)	.385
Grooved Pegboard - time preferred hand	76.3 (14.5)	74.7 (11.4)	.263
Grooved Pegboard – time non-preferred hand	82.4 (16.2)	77.6 (15.0)	.100
CPT – mean response time	403.3 (62.9)	379.0 (37.3)	.043
Visuospatial			
Hooper – total correct	26.3 (2.0)	26.7 (2.6)	.059
Stanford-Binet copy – total correct	5.1 (2.9)	5.3 (2.8)	.925
Rey-Osterrieth figure copy – total correct	26.4 (4.0)	26.6 (4.7)	.350
Memory			
CVLT – # correct trials 1-5	47.8 (9.5)	50.2 (9.7)	.599
CVLT – short delay # correct	9.9 (3.1)	11.0 (2.9)	.186
CVLT – long delay # correct	10.5 (3.0)	11.4 (3.3)	.251
CVLT – recognition # correct	14.4 (1.9)	15.1 (1.3)	.391
Rey- Osterrieth - immediate recall, # correct	16.3 (5.3)	17.8 (7.4)	.045
Rey-Osterrieth - delayed recall, # correct	15.3 (5.1)	16.9 (7.0)	.034
Stanford-Binet Recall - # correct	8.0 (2.7)	8.1 (2.3)	.765
General Intellectual Abilities			
WAIS-III information – raw score	21.7 (3.3)	23.4 (3.1)	.255
Mood and Motivation			
TOMM – total correct	48.7 (1.6)	49.4 (1.1)	.329

Task 3c. Exposure Assessment analyses for pesticides and PB will be ongoing.

Exposure assessment analyses of individual and combined classes of pesticides will continue to be conducted during years 3 and 4 to assess dose-response relationships with health and cognitive functioning. Mr. William Bradford, lead author of the Pesticides Environmental Exposure Report, will assist with these exposure estimates. Descriptive analyses for pyridostigmine bromide (PB) exposure based on total number of pills ingested as reported on the study questionnaire is presented in the table below.

Table 15. Pyridostigmine Bromide Exposure Categories for First 119 Study Participants

PB exposure		
	Frequency	**Percent**
No	**19**	**16**
Yes	**85**	**73**
Not Sure	**15**	**11**
Total	**119**	**100**
PB Dosage		
Total Tablets	**N**	**Percent**
0-5	**44**	**42**
6-20	**36**	**35**
21-40	**14**	**13**
41-90	**10**	**10**
Total	**104**	**100**

Table 16. PB dose-response analyses.

Test	Standardized Coefficients	t	Sig.
	Beta		
CVLT Trials 1-5	.118	1.05	.297
CVLT-long delay	.090	.808	.422
CPT- mean reaction time	.104	.582	.565
Trails A – total time	.082	.730	.468
Trails B –total time	-.068	-.602	.549
WCST- total sorts	.122	1.08	.284
Rey-Osterreith –delay score	.251	2.3	.024
Hooper –total correct	.183	1.7	.102
Stanford-Binet copy	.010	.09	.928

A preliminary analysis of PB dosage and neuropsychological patterns were largely non-significant as shown in table 16 with the exception of verbal recall as measured by the Rey Osterreith complex figure. However, this effect was not in the predicted negative direction but in the positive direction. The reported range of PB dosage suggests that further analyses of exposure levels will be possible when additional study subjects are recruited and higher statistical power is obtained. This will provide the ability to assess neuropsychological and health symptom reports in higher exposed individuals compared with those with less exposure in a dose-dependent manner. This will allow for comparison of synergistic effects of high PB and pesticide exposed individuals particularly with combinations of PB and other carbamates (bendiocarb, methomyl, and propoxur) and organophosphates (azamethiphos, chlorpyrifos, diazinon, dichlorvos and malathion). Individual pesticide exposures for the 12 pesticides of potential concern (see figure3) for the first 110 recruited study participants were categorized based on questionnaire reporting and past PCI interviews. The results are presented in the table below.

Table 17. Exposure Assessment for Pesticides of Potential Concern for First 110 Study Participants.

Pesticide	Low Exposed	High Exposed	Percent high Exposed
DEET	**63**	**47**	**43**
Permethrin	**82**	**28**	**26**
d-phenothrin	**104**	**6**	**5**
Azamethiphos	**77**	**33**	**30**
Chlorpyrifos	**80**	**30**	**27**
Diazinon	**84**	**26**	**24**
Dichlorvos	**74**	**36**	**33**
Malathion	**80**	**30**	**27**
Methomyl	**58**	**52**	**47**
Propoxur	**98**	**12**	**11**
Bendiocarb	**93**	**17**	**16**
Lindane	**72**	**38**	**35**

Additional analyses comparing individual pesticides of potential concern (POPC) with cognitive and health symptom reporting will be conducted as recruitment efforts progress and adequate statistical power is obtained.

Exposures ranged from 5 to 47 percent. Given that study participants were exposed to each of the 12 POPCs, it is feasible to study exposure to each of the pesticides of potential concern in this study sample.

Task 3d. Annual reports of progress will be written.

This report is the third annual report written for this project. The first report was submitted on February 28, 2005 and accepted on February 9, 2006. The second report was submitted on February 28, 2006 and accepted on July 7, 2006.

KEY RESEARCH ACCOMPLISHMENTS

- A pool of potential study participants was identified from a group of previously interviewed pest control personnel deployed to the Gulf War.
- Previous interviews by the Deployment Health Support Directorate (DHSD) regarding pesticide and pyridostigmine bromide (PB) exposure were obtained and used to classify these individuals into high and low exposure groups.
- Telephone interviews were performed and resulted in only a seven percent refusal rate of live calls and completion of the targeted 160 total completed exposure surveys of PCIs.
- Potential study participants were categorized based on current residence and re-categorized when residence changed.
- Current health symptoms were identified and categorized into symptom clusters based on initial telephone interviews.
- PCIs responding to the SRBI interviews were categorized into high and low exposure groups for pesticides and PB and a pool of potential subjects have been targeted for recruitment based on residence location and exposure category.
- One hundred and nineteen study participants were recruited and completed the entire study protocol including cognitive evaluations, psychological interviews and exposure questionnaires. This resulted in a 99% recruitment rate for years 1-3.
- The first 26 study recruitment trips were greeted with interest and willingness to participate by the contacted PCIs. This is encouraging for further recruitment efforts.

It appears that GW veterans continue to be interested in responding to surveys regarding health symptoms and are cooperative when asked to complete neuropsychological evaluations.

- It was determined that the study design allows for collection of all relevant data and can be accomplished in recruitment trips throughout the country.
- Initial exposure assessments of the 12 pesticides of potential concern (POPC) and pyridostigmine bromide (PB) suggest that analyses of individual pesticides with cognitive and health functioning should be possible when the larger study sample is obtained.
- Preliminary analysis of the first 110 study participants suggested lower mean reaction times, relative impairment in visual memory, and diminishment in executive functioning in high pesticide as compared with low pesticide-exposed veterans. In addition, the analysis comparing the interaction of high pesticide, high PB and Khamisiyah notification showed impairment in visuo-integration abilities in the group with concurrent exposures. These preliminary findings will be further explored in the larger study sample as participants continue to be recruited.
- Health symptom reports of the first 115 study participants using the health symptom checklist found higher symptom reporting in high pesticide exposed individuals relative to low pesticide exposure. Specifically, high exposure was related to GI disturbance, weakness, joint pain, word finding difficulty, sleep disturbance, skin rash and muscle pain. Individuals with Khamisiyah notification were significantly more likely to be diagnosed with irritable bowel syndrome than those without such notification. These elevated health symptom reports are much greater than the original SRBI telephone interviews where each PCI was asked to report their most prominent health symptoms or medical diagnoses. Medical diagnoses were higher in the high pesticide exposed group but not significantly so for most diagnoses. Overall,

this sample of GW veterans appeared to show slightly higher rates of asthma and allergies than reported in general population rates for their age and gender.

- Psychiatric diagnoses including post-traumatic stress disorder and current major depression were slightly elevated in this group of predominantly non-treatment seeking veterans while rates of chronic fatigue syndrome and multiple chemical sensitivity were relatively low when assessed by clinical interview.
- Data acquisition allowed for not only quantitative scoring systems, but also qualitative scoring of data in order to compare types of errors in cognitive performance. This type of subtle detail analysis has been correlated with neurotoxicant exposures in other investigations and will be compared as the larger study sample is recruited.

REPORTABLE OUTCOMES:

Publications

1. Pesticide Exposure, Health Functioning and Neuropsychological Outcome in Gulf War I Veterans (Abstract). Sullivan, K., Krengel, M., Thompson, T., Proctor, S.P. & White, R.F., International Neuropsychological Society, 34th Annual Meeting Program and Abstract Book, 2006: 208.
2. Cognitive functioning in Gulf War I veterans exposed to Pesticides, Pyridostigmine Bromide and Khamisiyah Weapons Depot (Abstract). Sullivan, K., Krengel, M., Thompson, T., Comtois, C., & White, RF. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 210.
3. Qualitative Findings in Complex Figure Drawing in Military Pesticide Applicators from the Gulf War. (Abstract). Sullivan, K., Janulewicz, P., Krengel, M., Comtois, C., &

White, R. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 209.

4. Proctor SP, Gopal S, Imai A, Wolfe J, Ozonoff D, White RF. Spatial analysis of 1991 Gulf War troop locations in relationship with postwar health symptom reports using GIS techniques. Transactions in GIS 2005; 9(3): 381-396.
5. Proctor, S.P., Heaton, KJ, Heeren, T. & White, R.F. Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US Army veterans. *Neurotoxicology*. 2006; 27(6): 931-939.

Invited Presentation

1. Krengel, M, Sullivan, K & White, R.F. Neuropsychological Functioning and Health Symptom Report in Pesticide and Pyridostigmine Bromide Exposed Gulf War Veterans. Stanford Research Institute, Palo Alto, CA, February 12, 2007.

Manuscripts in preparation: (from previous DOD funding sources)

1. Krengel et al., Longitudinal Health Symptom Report in Treatment-seeking Gulf War-era Veterans.
2. Proctor et al., Environmental and Occupational Exposure Predictors of Multiple Chemical Sensitivity in Gulf War Veterans Assessed via a Validated Screening Instrument.
3. Sullivan et al., Neuropsychological functioning in Gulf War veterans potentially exposed to chemical weapons at Khamisiyah, Iraq.

Planned Manuscripts:

1. Sullivan et al., Cognitive Functioning in military pesticide applicators from the Gulf War.
2. Krengel et al., Health Symptom Report in pesticide applicators from the Gulf War.

Funding:

1. In June 2004, Drs. White, Krengel, Sullivan, and Proctor submitted a Merit Review grant application (Dr. White PI) to the Department of Veterans Affairs entitled "Structural Magnetic Resonance Imaging and cognitive correlates in Gulf War veterans." This study will further define neurological functioning in a previously followed cohort of treatment-seeking GW veterans and will allow for comparison of reported GW exposures with brain white matter volumes. This grant was funded and recruitment efforts are underway. Preliminary results to date suggest lower anterior cingulate and overall cortical volumes in the high symptom Gulf War veterans compared with low symptom reporting GW veterans.

2. In September 2006, Drs. Krengel, Sullivan and White submitted a VA Merit review grant (Dr. Krengel, PI) to examine the continued health effects of GW veterans with cutting edge neuroimaging techniques in treatment-seeking GW veterans. This grant was not funded after the first submission. Dr. Krengel will resubmit this grant in March 2007.

3. In February 2007, Drs. Sullivan, Krengel and White submitted a grant to the DoD Gulf War Veterans Illness Research Program (GWVIRP) under the congressionally directed medical research program (W81XWH-06-GWVIRP) for a follow-up study to the currently funded study of military pesticide applicators in order compare structural brain imaging in the high and low pesticide exposed groups. This proposed grant will focus on whether acetylcholinesterase inhibiting pesticides including organophosphates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans by comparing objective biomarkers of exposed veterans and comparing brain white matter volumetrics between the groups.

CONCLUSIONS:

Preliminary results of neuropsychological analyses in the first 110 study participants indicated a significant effect of high pesticide exposure and lowered mean reaction times, executive system functions, and visual memory. In addition, health symptom reporting in high pesticide exposed individuals was significantly associated with gastrointestinal disturbances, skin rash, weakness, muscle pain, confusion and word-finding difficulty. When clinical diagnoses and health were compared, a slightly elevated rate of PTSD and depression were noted as well as asthma and allergies in both exposure groups. Overall, these preliminary findings of motor slowing, executive system and visual memory deficit, PTSD, depression, allergies and asthma in this group of higher exposed pesticide control military veterans suggests that clinicians treating GW veterans should consider these domains when assessing the health and functional well-being of these aging veterans. It is possible that these preliminary results reflect residual dysfunction attributable to neurotoxicant exposure from pesticides. However, this possibility will need to be re-assessed when the complete cohort sample is obtained.

Our preliminary findings from the SRBI interviews alone suggested that GW veterans exposed to varying levels of pesticides and PB continued to report health symptoms, including high blood pressure, cardiovascular disease, skin rashes, memory problems and stress reactions. These results were confirmed when more in-depth health symptoms were ascertained from the study questionnaire with the first 119 study participants. Of interest, veterans who participated in the SRBI telephone surveys reported significantly more physical than emotional symptoms. However, when interviewed in-person several of the study participants met clinical criteria for post-traumatic stress disorder and depression. This finding stresses the importance of face-to-face interviews and evaluations with study participants in addition to postal questionnaires or telephone surveys.

It still remains of particular clinical relevance that these veterans continue to report significant physical symptoms and by documenting changes in cognitive status in conjunction with health concerns in this unique group of Gulf War veterans, the effects of exposure to neurotoxicants while in the Gulf will be further elucidated. This study will be able to confirm or dispute the conclusion of the OSAGWI health risk assessment and the RAND pesticide report which suggested that the acetylcholinesterase inhibiting pesticides including organophosphates and carbamates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans by performing cognitive assessments with a group of military pesticide applicators with known chemical exposures.

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Appendix:

Reasoning, Symbol Search, Digit Symbol-Coding, WMS-III WordList, Verbal Paired Associates, and Logical Memory, Stroop, Cancellation H, Trail Making, COWAT, Fingertapping, Grooved Pegboard, and Dynamometer. Principal Components Analysis was performed to confirm domains of functioning assessed in these groups.
Results: Five factors with eigenvalues of 1 or higher explained 62% of the variance found in the welders group. These factors were consistent with the following domains: Immediate Verbal Memory, Delayed Verbal Memory, Attention and Executive Functioning, Mental Processing Speed, Motor Skills. All but one test had a factor loading above .5.
Conclusions: The short test battery used for screening welders with different exposure levels did assess the domains intended to be evaluated. Specific factor loadings for different tests will be shown.
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K.L. HANSON, M. LUCIANA & K. SULLWOLD. Reward-Related Decision-Making Deficits Among MDMA and Other Drug Users.
Objective: MDMA (3,4-methylenedioxymethamphetamine; Ecstasy) is a synthetic amphetamine derivative with mild hallucinogenic and stimulant effects. It is a known serotonin neurotoxin that may produce memory and executive dysfunction as well as impulsivity. However, few studies of MDMA users have examined reward-related decision-making, thought to be mediated by the ventromedial prefrontal cortex. Our aim was to examine reward-related decision-making among MDMA users, while considering the influence of other substance use via a polydrug control group.
Participants and Methods: Abstinent MDMA users (n = 22), other drug users (n = 30), and healthy non-drug controls (n = 29) completed the Iowa Gambling Task (IGT; Bechara et al., 2004), a neuropsychological battery, self-report measures of personality, and a comprehensive drug use interview.
Results: MDMA users and other drug users were similar on measures of cognition and personality; however, both drug use groups demonstrated poorer IGT performance and elevated impulsivity relative to controls. Among MDMA users, individuals who met DSM-IV substance use disorder criteria for MDMA (n=14) performed more erratically on the IGT relative to individuals without this diagnosis (n=8). Relationships between IGT performance, alcohol and drug use characteristics, and self-report measures of impulsivity were examined using Spearman's correlations.
Conclusions: Both drug use groups were at risk for reward-related decision-making deficits and elevated impulsivity, possibly due to a dysregulated serotonin system and/or ventromedial prefrontal cortex dysfunction. Individuals who abuse or are dependent on MDMA may have a particularly increased risk of executive dysfunction.
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J. JACOBUS, B.C. SCHWEINSBURG, A.D. SCHWEINSBURG, M.J. TAYLOR & I. GRANT. The Interactive Effects of Age and Alcoholism on Brain Response to Spatial Working Memory.
Objective: Previous studies have suggested age-related structural brain changes in alcoholism that differ from effects in normal aging. However, the functional correlates of this relationship have not been well characterized. In this study, we examined the interaction between age and alcoholism on FMRI response during a spatial working memory task, as this task has been shown to be sensitive to alcoholism-related brain injury across a wide age range.
Participants and Methods: Participants were 27 male recently detoxified alcoholics (RDA, abstinent 2 to 3 weeks; mean age = 46.2 ± 8.3) and 11 male controls (mean age = 45.6 ± 9.6) matched on age. FMRI data were acquired while participants performed a 2-back spatial location working memory task. Regression analyses predicted FMRI response from age, alcoholism status, and their interaction.
Results: Groups had similar accuracy and reaction times on the task. FMRI analyses revealed interactions between age and alcoholism in bilateral medial frontal, bilateral superior frontal, and right middle frontal gyri, medial precuneus/posterior cingulate, and bilateral cuneus (clusters > 943 microliters, $p < .05$). Simple effects regressions showed that RDA had a negative relationship between age and FMRI response, while controls showed a positive relationship between age and FMRI response.
Conclusions: These results demonstrate an age-related decline in FMRI response to spatial working memory among alcoholics, yet an age-related increase among controls. In healthy volunteers, neural effort may be increased in older age in order to maintain task performance. Yet in alcoholics, such compensatory responding is observed at a younger age, but this capacity may be limited in older alcoholics. One implication may be that older recently detoxified alcoholics may process information less efficiently, and thus could potentially have difficulty with complex everyday tasks.
Supported by a Veterans Affairs Merit Review Grant to Dr. Grant.
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K. SULLIVAN, P. JANULEWICZ, M. KRENGEL, C. COMTOIS & R. WHITE. Qualitative Findings in Complex Figure Drawing In Military Pesticide Applicators from the Gulf War.
Objective: Current hypotheses for the continued cognitive complaints in GW1 veterans invoke exposure to multiple neurotoxicants. Many neurotoxicants are known to affect the visuospatial domain. Therefore, the goal of this study was to evaluate the relationship of multiple chemical exposures and visuospatial functioning on the Rey-Osterrieth Complex Figure Test (ROCFT). By employing the Boston Qualitative Scoring System (BQSS), it was possible to provide an in depth analysis of performance by obtaining 6 summary scores and 17 qualitative scores of the ROCFT.
Participants and Methods: Study participants included a subgroup of 67 GW pesticide control personnel taken from a larger study of GW veterans. Pesticide control personnel were divided into 4 groups based on high and low exposure for pesticides and pyridostigmine bromide (PB). Each study participant completed the ROFCT according to standard administration and standard scoring of the BQSS. It was hypothesized that individuals with multiple chemical exposures (PB, pesticides) would perform significantly worse on the qualitative measures of the BQSS compared with veterans without such exposures.
Results: Multivariate analyses suggested overall group differences on the BQSS configural, cluster, detail, presence, accuracy, placement, and qualitative scores when comparing the four exposure groups of PB and pesticides.
Conclusions: These preliminary findings suggest that multiple chemical exposures in GW pesticide control personnel appear to have resulted in impairments in visuospatial functioning and visual memory as indicated by in depth qualitative scoring of the ROFCT. Further analyses with a larger sample size will help to further elucidate these findings.
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T. MCQUEENY, K. LISDAHL MEDINA, A.D. SCHWEINSBURG, M. COHEN-ZION, B.J. NAGEL & S.F. TAPERT. Effects of Alcohol and Marijuana Use During Adolescence on Hippocampal Asymmetry and Cognitive Functioning.

Objective: Memory deficits have been reported in adolescents with heavy alcohol and marijuana use, yet the impact of these substances on hippocampal development remains unclear. In addition, relationships between hippocampal asymmetry and memory function have not been explored in substance involved adolescents. This study examined relationships between right > left (R>L) hippocampal asymmetry and cognitive functioning in alcohol and marijuana using adolescents.

Participants and Methods: Participants (15-18 years-old) were 16 alcohol using (Alc) teens, 26 marijuana and alcohol using (MJ-Alc) teens and 21 demographically similar controls. Hippocampal volumes were obtained through manually traced structural magnetic resonance images. All data were collected after at least 2 days of abstinence from all substances.

Results: After controlling for age and intracranial volume, group differences in asymmetry were observed ($p < .02$). Post-hoc analyses revealed that Alc teens had greater R>L asymmetry ($p < .05$) than both controls and MJ-Alc teens, for which more L>R asymmetry was observed. Among controls only, individuals with more R>L asymmetry performed better on verbal learning ($r = .45$, $p < .05$) whereas superior visual memory performance was related to greater L>R asymmetry ($r = -.54$, $p < .01$).

Conclusions: Alcohol using teens exhibited greater right versus left hippocampal asymmetry than other groups. The functional relationship between verbal and visual memory and hippocampal asymmetry was abnormal among substance using adolescents compared to non-drug using controls. These findings suggest differential effects of alcohol and combined marijuana and alcohol use on the relationship between hippocampal morphometry and learning and memory performance.

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K.L. MEDINA, K.L. HANSON, A.D. SCHWEINSBURG, M. COHEN-ZION & S.F. TAPERT. Neuropsychological Functioning in Adolescent Marijuana Users: Subtle Deficits Detectable After 30 Days of Abstinence.

Objective: In adults, studies examining the long-lasting cognitive effects of marijuana use demonstrate subtle deficits in attention, executive function, and memory. However, since neuromaturation continues through adolescence, these results cannot necessarily generalize to adolescent marijuana users. Therefore, the goal of the present study was to examine neuropsychological functioning in abstinent marijuana-using and demographically similar control adolescents.

Participants and Methods: Data were collected from 65 adolescent marijuana users ($n=31$, 26% female) and controls ($n=34$, 27% female) aged 16-18. Extensive exclusionary criteria included independent psychiatric, medical, and neurologic disorders. Substance use information and neuropsychological assessments were collected after 30 days of monitored abstinence. Dependent variables were composite scores for: psychomotor speed, visuospatial skills, complex attention, story memory, verbal list learning, verbal fluency accuracy, planning and sequencing, and problem solving.

Results: After controlling for lifetime alcohol use and gender, adolescent marijuana users demonstrated significantly poorer planning and sequencing ability ($\beta = -.70$, $p < .002$), complex attention ($\beta = -.57$, $p < .05$), and slower psychomotor speed ($\beta = -.49$, $p < .05$) compared to demographically similar controls. No significant gender-by-group interactions were observed.

Conclusions: The general pattern of results suggested that even after 30 days of monitored abstinence, adolescent marijuana users continue to demonstrate subtle deficits in planning and sequencing, complex attention, and psychomotor speed compared to non-marijuana using teens. Thus, marijuana use during adolescence may negatively impact neuromaturation and cognitive development. Implications include the need for psychoeducation aimed at informing adolescents and parents of the potential long-term cognitive consequences of heavy marijuana use, as well as longitudinal studies to help rule out premorbid influences.

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A.D. SCHWEINSBURG, K.L. MEDINA, T. MCQUEENY, B.C. SCHWEINSBURG & S.F. TAPERT. An FMRI Study of Residual and Persisting Abnormalities in Adolescent Marijuana Users.

Objective: Research suggests recovery from the neurocognitive impact of marijuana use within a month of abstinence among adults. We previously demonstrated altered functional magnetic resonance imaging (fMRI) response to spatial working memory (SWM) in heavy marijuana using (MJ) adolescents after 28 days of abstinence, but the influence of recency of use has not yet been explored in detail. In this study, we compared fMRI response during SWM between MJ teens with brief and sustained durations of abstinence.

Participants and Methods: Participants were 15-18 years old, including 15 MJ teens (33% female) who had used 2-7 (mean=4) days prior to scanning (MJ-recent), and 15 MJ teens (27% female) who had been abstinent for at least 27 (mean=35) days (MJ-abstinent). Groups were similar on demographic and substance use characteristics, and had no psychiatric or medical disorders. Teens performed a SWM task during fMRI acquisition.

Results: Groups performed similarly on the SWM task, but MJ-recent showed more fMRI response in left superior and medial prefrontal cortices, bilateral insula, left superior temporal cortex, and right superior parietal cortex. MJ-abstinent had more response in the right precentral gyrus (clusters > 1328 microliters, $p < .05$).

Conclusions: Results show that recent marijuana using adolescents have more brain response than abstinent users during a spatial working memory task. Though cross-sectional, this evidence could suggest less compensatory neural response as the brain adjusts to the absence of marijuana through early abstinence. Longitudinal studies are needed to characterize the potential neural recovery during early abstinence from marijuana.

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K. SULLIVAN, M. KRENGEL, T. THOMPSON, C. COMTOIS & R. WHITE. Cognitive Functioning in Gulf War I Veterans Exposed to Pesticides, Pyridostigmine Bromide and Khamisiyah Weapons Depot.

Objective: One theory for the continued health complaints in GW I veterans is the combination of multiple chemical exposures. The goal of this study was to evaluate the relationship of the combined exposures of pesticides, pyridostigmine bromide (PB) and sarin on the cognitive functioning of GW I veterans.

Participants and Methods: Study participants included a unique group of 100 pesticide control personnel from the GW including pesticide applicators (high-exposed group) and preventive medicine specialists (low-exposed group). Each study participant completed a comprehensive battery of neuropsychological tests, psychological interviews and health symptom/exposure assessment questionnaires. It was hypothesized that individuals with high pesticide exposure would perform significantly worse on cognitive measures than a group of GW military personnel with low pesticide exposure. It was also hypothesized that multiple chemical exposures (PB, pesticides, sarin) would prove to be synergistic and/or additive in terms of decreased cognitive functioning.

Results: Preliminary results suggested that individuals with high PB and pesticide exposure who were also exposed to the Khamisiyah weapons depot detonations (and exposed to sarin from the explosions) performed more poorly on tests of visuospatial integration, visuoconstruction and visuospatial recall than the low exposure group.
Conclusions: These preliminary findings suggest that multiple chemical exposures in the Gulf theatre may have proven synergistic and resulted in impairments in visuospatial functioning. This finding of visuospatial functioning deficit is consistent with what has been documented with other known neurotoxicants.
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S.P. CERCY & M.M. WANKMULLER. A Case of Cognitive Dysfunction Associated with Elemental Mercury Ingestion.
Objective: To describe cognitive dysfunction associated with elemental mercury exposure.
Participants and Methods: A 63 year-old Caucasian man with a history of alcohol dependence ingested elemental mercury as a suicide gesture. One known prior admission for mercury ingestion occurred 4 months previously. He was treated with pro-motility agents and succimer chelation. Through discharge, serial abdominal X-rays showed gradual but incomplete clearance of mercury from the colon. Moreover, routine chest X-ray showed evidence of punctate radiopaque materials in the posterior lower lobe of the right lung. Neurological examination revealed no characteristic evidence of mercury intoxication. Blood mercury levels peaked about 10 days following admission and declined thereafter; urine mercury levels were highest at discharge. Both were well in excess of thresholds considered to be associated with cognitive dysfunction. CT of the head showed mild atrophy. Given the history, he underwent neuropsychological assessment.
Results: Neuropsychological evaluation revealed deficits most prominently affecting cognitive speed, flexibility, and response inhibition. Semantic fluency, visuospatial processing, and recall memory for visual and low-context verbal material were also affected. Behaviorally, affect was irritable, speech volume was increased, and there was a mild upper-extremity action tremor.
Conclusions: Deficits may be attributable primarily to chronic alcohol abuse. Elemental mercury typically is not readily absorbed by the GI tract and does not easily cross the blood-brain barrier. However, in this case, mercury apparently volatilized and was inhaled. Mercury vapor is lipid-soluble and readily crosses the blood-brain barrier. Moreover, high urine and blood mercury levels were found. Therefore we argue that mercury intoxication may have been a factor contributing to the patient's cognitive dysfunction.
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Endocrine Disorders/Hormones

L.H. RUBIN, K.L. MORDECAI, M. BACCOZINO, J. PELLEGRINO & P.M. MAKI. Effects of Ovarian Steroid Hormones on Components of Phonemic Fluency in Premenopausal Women.
Objective: Research demonstrating a female advantage on verbal fluency tasks and enhanced performance during the midluteal (high estrogen and progesterone) phase of the menstrual cycle suggests that estrogen can enhance verbal fluency. The cognitive processes that could explain this relationship are unknown. Verbal fluency tasks are influenced by two processes: clustering (automatic temporal process) and switching (controlled frontal process). We examined these processes across the menstrual cycle and with oral contraceptive (OC) use. Total words and clusters were expected to be enhanced during the midluteal compared to the follicular phase (low estrogen and progesterone) for non-OC users. Given that OC enhances exogenous estrogen levels, superior performance on total words was expected for OC users.
Participants and Methods: Sixteen women on OCs and 13 women not on OCs completed verbal fluency tests during their midluteal and follicular phases. Outcome measures included total words generated, mean clustersize, and total switches on phonemic fluency.
Results: As expected, Users produced more words and switches than Nonusers. Counter to predictions, women generated more words and larger clusters during the follicular compared to the midluteal phase. The phase effect on phonemic fluency was no longer evident in an analysis covarying for clustering. Estradiol correlated with switching during both phases in Nonusers.
Conclusions: As predicted, OC users showed enhanced verbal fluency, but the pattern of change across the cycle was opposite predictions. It may be that high levels of endogenous progesterone are associated with decreased verbal fluency and decreased temporal function.
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S. WRIGHT, B. GIORDANI, S.A. LANGENECKER, J.M. BENO, K. GUIRE, E.M. BRICENO, B.D. LONG, D.E. SCHTEINGART & M.N. STARKMAN. Cognition Following Successful Surgical Intervention of Cushing's Disease.
Objective: Cushing's disease (CD) provides the opportunity to investigate the effects of hypercortisolism, as well as the potential reversal of these effects following treatment. Previously, we demonstrated impairments in executive functions and verbal and visual learning in a group of CD patients prior to surgical intervention. For this study, we compared pre-surgical performance in these cognitive domains with performance at up to 18 months following successful surgery. We hypothesized that CD patients would demonstrate improvements post-surgery across the cognitive domains measured as compared to their performance prior to surgical intervention.
Participants and Methods: Twenty-two CD patients, aged 10-59, received the same battery of neuropsychological measures pre- and post-transsphenoidal surgery with remission of hypercortisolism.
Results: Using repeated measures ANOVA, we found that patients demonstrated significant improvement on measures of verbal and visual learning following surgical intervention (all ps < .05), consistent with earlier findings by our group. Measures of executive functioning did not significantly improve.
Conclusions: These findings suggest that not all cognitively impaired areas improve in the months following successful surgery. Some areas, such as executive functioning, may take longer to recover or never improve. The hippocampus, an area dense in glucocorticoid receptors and important for memory functioning, may recover more quickly than other regions of the brain following improvement of cortisol levels. Other areas of the brain also rich in glucocorticoid receptors and associated with executive functioning, such as prefrontal cortex, may respond to reduced cortisol more slowly. Potential modifiers of post-surgical changes, including depression level, age, and time since treatment are explored.
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